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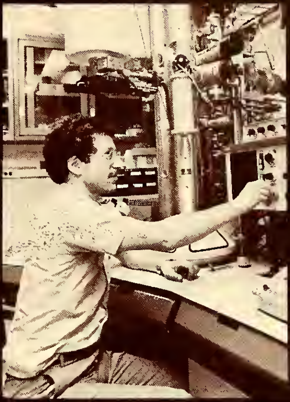
Division of Research Services



Annual Report
Fiscal Year 1983

National
Institutes
of Health

A Letter From the Director

Joe R. Held, D.V.M., Director
Division of Research Services
National Institutes of Health (U.S.)
DC Division of Research Services.

(Annual report)

Like the other components of the National Institutes of Health, the Division of Research Services in Fiscal Year 1983 continued to operate within the constraints of a tight budget. For DRS this presented the challenge of maintaining its high level of service to NIH intramural research and the greater challenge of continuing to improve its services under these constraints.

The following reports from the four branches of DRS show how they have met this challenge. The various improvements introduced during Fiscal Year 1983 are enabling DRS to do an even better job of providing NIH intramural investigators with services and products needed for planning, performing, and reporting their research. A few samples from the DRS branch reports illustrate this effort.

In the NIH Library, far-reaching improvements under way had a highly visible expression: the construction of a computer room and installation of the computer and terminals. These will serve the Library's on-line catalog and circulation systems beginning early in FY 1984. The less visible preparations for complete automation of the Library's services were equally important: for example, conversion of the catalog to machine-readable form for integration of the catalog and circulation systems, so that an NIH investigator checking a catalog item can simultaneously determine its current availability.

The Veterinary Resources Branch this year began to offer a service which the Branch had long desired to provide for NIH investigators: holding of rodents and rabbits on experiment, in either a conventional or gnotobiotic setting. The researchers have access to their animals in the holding facility. VRB renovated its Building 14B so it can offer this service, which complements the Branch's long established service of holding large animals for intramural investigators.

The Branch's Genetic Monitoring Laboratory, which since 1978 has played a key role in verifying the genetic integrity of the defined inbred strains of rodents produced in the VRB, continued to refine its methods. Only one microliter of antisera is needed for the Laboratory's modified microcytotoxic test, developed for typing a variety of cell surface antigens in VRB's inbred mice. Work is also proceeding on development of polyclonal alloantisera; this may provide a more efficient means of screening production colonies of mice for genetic contamination. As researchers become more aware of the threat genetic contamination could pose to the validity of their findings, the important of the VRB genetic monitoring program is all the more obvious.

Improvements in research and clinical methodology are part of the very mission of DRS's Biomedical Engineering and Instrumentation Branch, along with services to promote the smooth functioning of scientific instruments in use here. BEIB engineers this year continued to collaborate with NIH intramural programs on a wide range of developmental projects including work on NMR imaging, PET scanning, flow cytometry, ultrasound, fiber optics, electro-optics, calorimetry, electron beam imaging and microspectroscopy, fluid mechanics, magneto-encephalography, and analytical methods.

An important landmark in these efforts occurred this year: the first tests in humans of a new miniature toposcopic catheter for localized delivery of chemotherapy to patients with inoperable brain tumors. This minimal-friction catheter was under development in BEIB for several years.

The Medical Arts and Photography Branch has focused much of its attention this year to keeping costs down despite the pressures of inflation. Some economics, however, are also improvements. For example, MAPB arranged to enlarge its computer graphics capacity by obtaining the Xerox-350 Color Slide System for producing computer-generated slides. Besides producing slides at lower prices, this system eliminates the need to store board art, since the information is stored on a floppy disk. Revised slides can be prepared by modifying the disk, and the system also produces black-and-white slides from which prints can be made for journal publication.

To provide intramural investigators with timely information about DRS services and products—especially new ones—the Division has begun distribution of "Research Services Updates." The first issue highlighted scientific equipment fabrication projects in the Biomedical Engineering and Instrumentation Branch and new services available from the Small Animal Section of the Veterinary Resources Branch.

DRS began work this year on an *ad hoc* project for program improvement: evaluative studies of four selected DRS branch operating procedures, to be performed by outside reviewers during FY 1984. Many internal management studies will also be completed in an attempt to reduce costs and coordinate Division-wide activities; these DRS studies include (a) use of word processors and personal computers, (b) utilization of the NIH Library, and (c) the most appropriate method for repairing and maintaining scientific equipment. A similar internal management study this year led to a 20 percent reduction in overtime, which brought a cost savings of $90,000.

The DRS Fiscal Year 1983 budget increased by 2.5 percent over FY 1982 actual obligations. This level of increase is inherent to the continuing cost saving measures the Division is taking without adversely affecting our support of the NIH scientific community.

As the accompanying chart indicates, DRS is funded through both of NIH's program support budget mechanisms: the Service and Supply Fund (SSF) and the Management Fund (MF). The SSF operates on a fee-for-service basis; specific customers are identified and charged as would be done by a business firm. This is an excellent mechanism in cases where a discrete service or product can be measured easily. During the past 10 years, the DRS budget has gone from one-third to two-thirds SSF financing. Activities in which a discrete service or product cannot easily be measured are supported by the MF, which consists of assessments based on the dollar value of the intramural research budget of each NIH Bureau, Institute, and Division (BID).

A special feature of this year's DRS Annual Report is a discussion of the Assistant Secretary for Health's transformation of the Interagency Primate Steering Committee into the Interagency Research Animal Committee (IRAC). As the committee's executive director, Dr. Thomas Wolfle, explains in that paper, the action meets the need for a Federal intergency committee knowledgeable about the conservation, use, care, and welfare of research animals, and representative of all the Federal agencies utilizing a considerable number of them. The Director, DRS, serves as chairman of IRAC, and the DRS Veterinary Resources Branch provides administrative support, including the services of the committee's executive director. Dr. Wolfle's paper follows the report of the Veterinary Resources Branch.

Division of Research Services FY 83 Budget (in thousands of dollars)

Branch	Management	Service & Supply	Total
Veterinary Resources	$4,434	$7,539	$11,973
Biomedical Engineering & Instrumentation	2,821	5,984	8,805
Library	3,018	-	3,018
Medical Arts & Photography	587	4,302	4,889
Total	$10,860	$17,825	$28,685

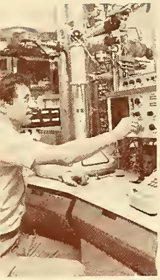
Publications

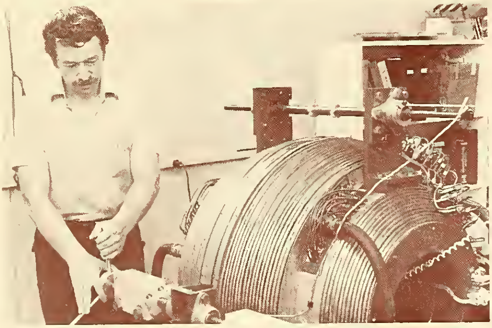
Held, Joe R.: Animals in research: an international overview. *California Veterinarian* 37 (1): 93-95, 1983.

Held, Joe R.: Appropriate animal models. In Sechzer, Jeri A. (Ed.): *The Role of Animals in Biomedical Research*. New York, The New York Academy of the Sciences, 1983, pp. 13-19.

Held, Joe R.: Conservation and management of nonhuman primates, *Microbiologia* 5: 161-169, 1982.

Held, Joe R.: Nonhuman primates, their use in biomedical research. In Kalter, S.S. (Ed.): *Viral and Immunological Diseases in Nonhuman Primates*. New York: Alan R. Liss, 1983, pp. 3-16.





Work in progress in the Biomedical Engineering and Instrumentation Branch (from top down):

An electron microscope automated to produce full color maps showing locations and concentrations of atomic elements in tissue.

Lip motion transducer produced for NINCDS speech studies.

Special purpose video preamplifier which provides improved imaging and ease of use.

Electromagnet serving as part of an NMR imager of advanced design.

NASA isothermic suit specially instrumented by BEIB for collaborative studies with NIMH on effects of isothermia on sleep.

Biomedical Engineering and Instrumentation Branch

Murray Eden, Ph.D., Chief

"Above all, do no harm" is one of the oldest of medical sayings; it continues to inspire the search for means of diagnosis and treatment that do the least incidental harm. The Biomedical Engineering and Instrumentation Branch (BEIB), NIH's focus for expertise in engineering and related sciences, has recently completed six years of developmental effort on a catheter whose advanced design approaches that ideal.

The problem has been how best to advance catheters through narrow, twisting blood vessels to remote sites in order to diagnose or treat. Traditionally, catheters have slid into blood vessels, and this has been the "rub." Friction between the catheters and blood vessel walls tends to catch or buckle the catheters or, even worse, induce vascular spasm. Doctors could, of course, push harder on stiffer catheters to force them past obstructions, but such catheters would be too inflexible to negotiate sharp turns and might damage the blood vessels in the attempt.

BEIB's catheter avoids these problems. Instead of sliding relative to vessel walls, it advances like tank tread, laying itself in place, until it's time to retract—when it simply picks itself up.

Engineers in BEIB's Mechanical Engineering Section have based their catheter on a concept that Zeimer and Simkin first described in 1966. That catheter had a diameter ten times greater than today's version and was intended for use in the gastrointestinal tract. Like the original catheter, BEIB's miniature verson is tucked into itself like a rolled-up sock. When physicians apply pressure to the end that is outside the body, the catheter advances with minimal friction by continuously everting itself. Much lower pressure causes the catheter to retract. In tests the catheter has passed easily through simulated, tortuous vessels which other catheters could not negotiate, and it has been successful in the external carotid, vertebral, hepatic, renal, and coronary arteries in dogs.

More recently, BEIB and the Diagnostic Radiology Branch (DRB) of the NIH Clinical Center, tested the catheter in humans for the first time. The catheter delivered the drug BCNU to an inoperable brain tumor in a very localized manner, resulting in fewer side effects. The DRB and the Surgical Neurology Branch of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) have begun to treat a series of patients in this way.

Similarly, BEIB has been working on several other projects that improve diagnosis or treatment while minimizing risks. One of these, BEIB's effort to produce a diagnostic imager based upon the principles of nuclear magnetic resonance (NMR), produced its first image this past year. The image, that of a thin piece of plastic pierced by wells containing manganese chloride, showed details as small as 0.7mm. Moreover, the team that developed the imager made novel use of the technique of parallel processing to dramatically shorten the time that a computer needs to create an image.

In conjunction with the NIH Office for Medical Applications of Research, the Branch sponsored a Consensus Development Conference on "Clinical Applications of Biomaterials" at the NIH, November 1-3, 1982. The conference brought together approximately 350 physicians, dentists, polymer scientists, surface chemists, biochemists, materials scientists, metallurgists, chemical and biomedical engineers, mechanical engineers, microbiologists, lawyers, government officers, and consumers. After two days of formal presentations by leading experts in various areas, a panel of 16 members from a variety of backgrounds—including those of industrial and academic research—addressed several questions:

- How safe and effective are biomaterials currently in clinical use?
- How well can we predict biological performance of materials in the human body, including host response, and biomaterials response?
- What results of ongoing research in materials science would be potentially applicable to clinical care?
- Are the ways for introducing biomaterials into medical use responsive to current clinical needs? Which elements in the process are amenable to improvements?
- What are the areas of greatest clinical need for new biomaterials?

The panel deliberated, discussed its findings with the conference attendees, and adopted a statement that summarized the conclusions on the issues. This statement has been distributed to

20,000 individuals and organizations, including the major medical libraries, medical schools, the medical industry, the Society for Biomaterials, and interested laypersons. Further, the statement appeared in the *Journal of the American Medical Association* and the *Journal of Biomedical Materials Research.* Full papers by the conference participants will be available as a book, *Contemporary Biomaterials.*

The Branch has also been quite busy fulfilling its commitment to provide the NIH research community with a broad range of scientific and engineering expertise. For example, BEIB has collaborated in more than 200 projects to produce advanced instrumentation, models, methods, and techniques dedicated to the acquisition of biomedical information previously unavailable to NIH's scientists.

The staff of 45 professional physical scientists and engineers and 81 technical support personnel responded to over 3,000 requests for the fabrication and modification of laboratory devices and made another 9,800 repairs and minor changes of scientific equipment.

In addition, BEIB is cooperating with the government of Egypt and the governments of several Caribbean nations to increase their capability to maintain hospital and scientific equipment. Funding for these projects is provided by the U.S. Agency for International Development (AID). In each of these projects BEIB and AID are attempting to establish self-sustaining programs able to train new personnel and modify operations to meet changing needs after BEIB's participation in the programs ends.

BEIB's professional staff functions within four sections and the Office of the Chief. Here is a brief description of their activities in FY 1983.

Applied Clinical Engineering Section (ACES)

This group, composed of biomedical, mechanical, and electronic engineers and a complement of engineering technicians, is located in the Clinical Center/ACRF complex. It offers broad expertise suitable to wide varieties of collaborations in biomedical research. For example, the group is working alongside the Clinical Pharmacology Branch of the National Cancer Institute to refine procedures for flow cytometry that are integral to ongoing studies in cell kinetics. One result has been the design and incorporation of a triple-laser flow system into an existing flow cytometer. This unique device measures three cell parameters simultaneously, thus conserving precious clinical samples and hastening their evaluation. Preliminary experiments have demonstrated the success of the system; the data obtained show that the modified device has an improved coefficient of variation—particularly for signals with low fluorescence.

Members of this group are also involved in the development of mathematical models of tumor growth in which tumors compete for resources. Additionally, using its flow cytometry equipment as a model, the ACES has developed a computerized method to evaluate the effects of optical components on signals transmitted by light. The spectral properties of fluorescent dyes, optical filters, ion laser emissions, and photomultiplier tubes are compiled from various sources and manipulated mathematically so that all spectra are in the same format. The computer algorithm then models the effects of the individual optical components on the signal. Researchers can compare the output of the model to actual signals and use the results as an aid in choosing optimal components for flow cytometric systems or any system that uses light to transmit signals.

Another fruit of this collaboration has been the derivation of novel analytical procedures for processing DNA histograms. The first is a decomposition of Gaussian errors from the DNA histograms, which reveals the presence of different cell populations that may be present in the preparations. The second procedure is a count-dependent filter that compensates for regions of the DNA histogram with insufficient data to faithfully represent signals. The ACES is modifying this filter slightly for an additional use in the Nuclear Medicine Department of the Clinical Center to improve camera images from beta scans.

The ACES is also collaborating with the Laboratory of Parasitic Diseases of the National Institute of Allergy and Infectious Diseases (NIAID) in flow cytometry experiments designed to understand better the kinetics of certain protozoans. This particular situation has involved the modification of electronic and computer circuits in order to modernize data acquisition and data analysis in flow cytometry. The Clinical Pathology Department of the Clinical Center has also requested that the Section enhance the Clinical Center's newly purchased Epics V cell sorter and cell cytometer.

Over the past year, the Applied Clinical Engineering Section and the Rehabilitation Section of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) have collaboratively used novel instruments to diagnose and treat certain speech disorders. The Section has provided engineering support to the nearly completed speech laboratory in the Ultrasound Department of the Clinical Center. Furthermore, support of the Acoustics Lab, NINCDS, has resulted in the development of a first and second generation device which monitors lip movements in all three anatomic planes. The first model used an infrared detection technique to sense the movement of rotating cams coincident with the movement of the lips. The second model employs a new photo-optical technique developed by the ACES to detect these motions differentially, thereby eliminating errors of electronic drift. The second model is also significantly lighter, due to simplicity of the optical detection circuitry and careful design of the transducer housings.

Last year, ACES and the Laboratory of Animal Surgery of the National Heart, Lung, and Blood Institute (NHLBI) continued to refine techniques for oscillometric blood pressure measurements. By incorporating earlier experimental results, the project has led to the design and construction of a patent-pending blood pressure cuff. Concomitant efforts are directed toward better understanding of the relationship between the mean arterial pressure and associated oscillometric pressure waveforms.

The Heart Surgery Branch of the NHLBI and ACES have developed an improved Left Heart Assist Device (LHAD) that does not draw a negative pressure. This eliminates the problem of outgasing associated with drawing blood through an intramyocardial catheter. The pump is portable and facilitates the weaning of surgical patients from the heart-assist procedure.

Continuing studies with the Surgery Branch of the NHLBI have resulted in some useful findings on the protective effect of various substances on ischemic myocardial tissue. An isolated heart perfusion apparatus developed by ACES and the Surgery Branch enables study of the heart's efficiency by measurement of its physiological parameters. The apparatus allows *in vitro* monitoring of working hearts during ischemia and recovery from cardioplegia. The collaborative team has also used the system to measure biochemical parameters of cardiac tissue using the fiber optic pH probe designed by BEIB's Chemical Engineering and Mechanical Engineering Sections.

In collaboration with the Psychobiology Laboratory of the National Institute of Mental Health (NIMH), the ACES is studying the effects of body temperature manipulation on circadian rhythms of sleep and blood hormone fluctuations. The team expects to gain insight into underlying physiological mechanisms by modifying normal rhythms of body temperature.

With the Cancer Surgery Branch of the National Cancer Institute (NCI), the ACES is studying preoperative and postoperative metabolic measurements. The measurements will increase understanding of the pathophysiology of cachexia in patients with sarcoma. In this study the team will use calorimetry to measure the metabolic demands that tumors place on patients with cancer, including resting energy expenditures and the mechanism of host-tissue depletion. The ACES has also begun experiments with the Laboratory of Technical Development, NHLBI, to determine parameters of endotherma and exothermal chemical reactions, using microcalorimetric instruments initially developed by BEIB's Mechanical Engineering Section.

ACES and the NIAID are designing equipment capable of providing well-controlled heat for treatment of extremities infected by Leishmaniasis. Previous efforts have established that the hyperthermia method is useful; however, the equipment previously used has been water-based and bulky. A totally electric device with suitable safeguards will be designed as a replacement.

Additionally, ACES is providing necessary engineering support to the patient care areas of the Clinical Center/ACRF. The emphasis is on programs for preventative maintenance of patient care equipment, checks of electrical safety for equipment and patient care areas; investigating failures of biomedical equipment, and teaching personnel about hazards of equipment and the proper use of technology for patient care.

Chemical Engineering Section (ChES)

The Chemical Engineering Section has continued to strengthen its competence in synthetic membrane technology for application to biomedical research and clinical medicine. Synthetic membranes offer considerable potential for a variety of applications, including use in tissue cultures, various types of separation technology, and specialized instrumentation. The Section has increased the understanding of membrane transport by using thermodynamic and hydrodynamic theories to predict simultaneous, coupled convective and diffusive transport across porous membranes. ChES has also applied membrane technology to instrumentation, such as membrane-based sampling systems for kinetic studies and membrane chambers for studies of cancer cell sensitivity *in vivo*. Cells may be recovered easily for biochemical or cytokinetic observations, and appropriate choice of the membrane can provide an immunologically privileged sanctuary to uncouple pharmacologic from biological responses.

Of particular note, one Section member organized and directed a course, the Advanced Study Institute on Synthetic Membranes, sponsored by the Scientific Affairs Division of the North Atlantic Treaty Organization (with supplemental support from BEIB, the National Science Foundation, and several companies active in the field). This was a two-week intensive course presented by 16 internationally-known experts to more than 60 participants from more than 17 countries. It provided instruction for participants and interaction among scientists and engineers from various geographic, institutional and scientific backgrounds. The curriculum covered membrane synthesis, membrance characterization, transport principles, membrane processes, engineering design and optimization, and a variety of areas of current research and promising application to biomedicine and biotechnology.

The Section is using chemical-reaction engineering to describe and predict the concentrations of drugs and other chemicals in the body. These substances are typically tested in experimental animals with the objective of extrapolating results to humans. At issue are both the risks associated with environmental contaminants and the optimization of chemotherapy. The Section has developed pharmacokinetic theory for drug infusion into a tumor or tumor-bearing region, combined with extracorporeal removal of the drug before it returns to the body. The prototype catheter that BEIB's Mechanical Engineering Section developed and the availability of equipment to remove drugs from venous blood make this concept feasible for the treatment of brain tumors; it is now beginning a clinical trial.

The Section is developing pharmacokinetic theory to describe the rather complex chemical reactions in the body thought to mediate the toxic or therapeutic effects of drugs. Emphasis continues to be placed on the "mouse-man" problem and, increasingly, the "test tube-man" problem as science's understanding of biological processes improves and we are able to apply results from *in vitro* studies to pharmacokinetic predictions. BEIB is also very interested in the mechanisms by which chemicals diffuse through and react with tissue. The great importance of regional drug administration has required a deeper knowledge of such diffusion-reaction problems. In a collaborative effort with BEIB's Electron Beam Imaging and Microspectroscopy Group, the Chemical Engineering Section has been able to obtain preliminary information on the distribution of platinum (from a platinum-containing anticancer drug) in the tissues surrounding the peritoneal space.

Experimental fluid mechanics and instrumentation are continuing areas of activity. A particular note is a collaboration among NIH, the American Red Cross, and the U.S. Food and Drug Administration intended to elucidate the effect of fluid shear on endothelial cells in culture. Flowing blood can have a direct mechanical effect on blood vessel walls. It can also affect wall properties by mediating the interactions between blood components, such as proteins and platelets, and the luminal surface. Exposure of endothelial cells to known fluid shears in a test cell permits observation of morphological, cytoskeletal and metabolic changes in the cells under well-characterized conditions. Instrumentation projects included (1) a fiber-optic oxygen probe for *in vitro* or *in vivo* studies, which uses fluorescence quenching to provide an equilibrium measurement of oxygen tension, and (2) a modified protein sequencer, which provides structural information on extraordinarily small amounts of protein.

Electrical Engineering Section (EEES)

The Electrical and Electronic Engineering Section continued its program of support of the NIH intramural reseach programs substantially as in past years, except that an increased emphasis on electro-optics, initiated several years ago, is now a significant aspect of the Section's activities. Some of the original instruments developed are now being used in a variety of applications. For example, several clinical protocols have been developed for use of a laser-doppler apparatus which measures peripheral microcirculation of blood. NIAID researchers are measuring nasal circulation to quantitate the effects of airborne allergenic agents as well as to develop dose-response curves for vasoactive drugs. They are also using it to study cold-induced asthma, in conjunction with a Pelletier cooler developed this year to control skin temperature. NHLBI is using the apparatus to study several aspects of sickle cell anemia, including the efficacy of drugs and transfusions and the impact of cold challenge, and NCI is using it to assess the vitality of skin flaps.

Another major instrument continuing to receive support is a device which automatically and non-invasively measures the quality and concentration of platelets in transfusion bags. The device uses a sophisticated adaptation of nephelometry as well as powerful microprocessor-based signal analysis. Clinical trials begin soon.

Two other projects approaching maturity are an electro-optic polarization system for the Division of Computer Resources and Technology that allows 3-D viewing of computer-generated moving pictures showing the conformation and interaction of biomolecules, and major modification of a commercial micro-spectrofluorimeter being used by NHLBI researchers to study renal cells. The modifications provide higher resolution and a new mode of operation: two-dimensional total fluorescence. The Section also modified the video output to make it compatible with standard video tape recorders and monitors.

Several new optical projects are developing in collaboration with researchers of the National Eye Institute (NEI). The team has established the feasibility of using a CO_2 laser to perform vitrectomies and has determined optimum parameters for the laser employed. Work is continuing on probe designs as well as work with industry and the FDA to promote safe, effective, and expeditious commercial development. The use of high-power pulsed lasers for other types of ocular surgery, such as preoperative procedures for cataract surgery, is being studied to establish damage thresholds and optimum pulse-train parameters. Senile macular degeneration is also being studied with particular reference to the hypothesis that it may be induced by sunlight.

The Section has also devoted considerable effort to several projects involving imaging. One has involved the interconnection of a commercial system for optical-imaging analysis to two types of scanning electron microscopes, resulting in a system suitable for quantitating the efficacy of anti-cancer drugs against tumors grown on brain tissue. Similarly, the Section continued to support BEIB's analytical electron microscope.

The positron emission tomography scanner, developed over a period of several years in collaboration with the National Institute of Neurological and Communicative Disorders and Stroke and BEIB's Mechanical Engineering Section, was brought to its final seven slice capability and is in routine use; about a dozen clinical protocols have been developed so far. Considerable work remains in the areas of documentation, evaluation, and scatter correction. Scatter problems become serious for any high-resolution, high-sensitivity scanner and, accordingly, these have led to the development elsewhere of quite sophisticated correction techniques based on deconvolution with a spatially variant kernel. However, such an approach degrades signal-to-noise ratio, fails to accurately accomodate the distribution of the scattering coefficient, and does not explicitly exploit the information about scatter that is obtainable via energy analysis. The Section plans an effort to use this information, together with the known characteristics of the scattering process, to develop a correction based upon linear algebra that may be more satisfactory than deconvolution.

Microprocessor-based "smart" instruments continue to be a major area of interest. The Section has developed a portable, programmable infusion-pump controller for the National Institute of Child Health and Human Development (NICHHD) to facilitate the study of different administration schedules for anti-depressant and other drugs. In collaboration with researchers at the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), the Section has build a memory-challenge system for use with patients immediately prior to PET scanning. The effect of the memory challenge on neural metabolic activity will help elucidate some of the effects of alcoholism. The Section has applied microprocessor-based methods in the development of a fermentation system for the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK). Because of the use of a microprocessor, the parameters monitored and controlled can be changed at will to optimize yield and purity.

Other projects of interest currently under way include an NMR system for measuring water transport phenomena in squid axons, an improved data acquisition system for the BEIB ultracentrafuge, and improvement in the speed and sensitivity of a system for predicting intracellular parameters from extracellular measurements.

Perhaps the largest new project undertaken this year is an effort to obtain noninvasively a real-time 3D display of neural activity in the human brain. This has been under discussion with the staff of the Epilepsy Branch, NINCDS, for several years, but the problem of obtaining useful depth resolution from surface EEG signals appeared insurmountable. However, magneto-encephalography, a new technology utilizing superconducting quantum interference devices to detect the minute magnetic fields generated by neural currents, appears to hold promise and is being actively explored. Even if the required information can be obtained noninvasively, however, the problem of processing and displaying it satisfactorily is still a formidable one—but is becoming more manageable with the advent of array processors. Our efforts will initially be directed to the problem of localizing the sites of epileptic foci.

Mechanical Engineering Section (MES)

The Mechanical Engineering Section conducted a wide variety of projects this year involving analytical and experimental studies and hardware development. As mentioned in the opening of this BEIB report, this year witnessed the highly successful use of the Mechanical Engineering Section's miniature toposcopic catheter to deliver chemotherapy in a localized manner to patients with inoperable brain tumors. In addition, the MES in collaboration with the Radiation Oncology Branch of NCI is developing a regional hyperthermia system for the adjunctive treatment of cancer. This research effort involves (1) the optimization of a "helical coil" RF applicator for the delivery of electromagnetic energy to deep-seated tumor masses; (2) the development of advanced types of perfused, heterogeneous phantoms for the *in vitro* characterization of the helical coil applicator and temperature-monitoring systems; and (3) the development of multidimensional bio-heat transfer models for the *a priori* prediction of thermal profiles based upon variation in anatomy, physiology, and tumor size. It is hoped that these *in vitro* studies will soon permit the development of a computer-controlled hyperthermia delivery system for use on human extremities. If the initial series of clinical trials is successful, NCI and BEIB will adapt the system to aid in the treatment of cancers found in more inaccessible areas of the human body, such as the thoracic and abdominal cavities.

In collaboration with the NHLBI, a theoretical model has been developed which for the first time successfully predicts the changes in the contour of the blood pressure pulse as it propagates through the brachial arterial system. The model predicts how the caliber of the side branches and the stiffness of the main artery affect the modulation of the dichrotic wave. The results agree with clinical observations of the effects of age and high blood pressure on responses to pharmacologically-induced vasoconstriction and vasodilation.

Working in collaboration with the NINCDS, the MES is developing a system for automating the three-dimensional reconstruction of small neural networks. The Section has designed a unique miniature microtome that fits within the specimen chamber of a scanning electron microscope (SEM). First, the microtome removes embedded tissue sections; then the SEM images the remaining block face, eliminating problems associated with making individual sections. After the section is removed, the microtome etches and gold coats the block faces *in situ,* preserving perfect image registration from section to section and delivering excellent picture quality. Oxygen plasma has been found to be an excellent, artifact-free etching medium compatible with the SEM. Miniaturization of the etching and coating devices is proceeding at this time, and completion of this phase will allow evaluation of the complete technique.

In another instrumentation area the Section has had substantial progress on a servo system for NHLBI which will control phasic aortic blood pressure in an awake closed-chest dog. The Section has bench-tested the hardware and will shortly test the device in animals. For the Clinical Center, the Section completed a computerized system for measuring the magnitude and direction of forces produced by the fingers. This will provide objective data for rehabilitation protocols. Also, working with NINCDS, the Section has begun development of novel technique to assess intracranial pressure and, working with NCI, it is developing a novel valve to control incontinence.

Theoretical studies are also under way concerning the constitutive equations describing the contraction of skeletal and heart muscle, the mechanics of bladder contraction, and the mechanics of the left ventrical and its interaction with the large arteries.

Analytical Methods Group

Members of the Analytical Methods Group in the Office of the Chief, BEIB, have pioneered in the development of physico-chemical techniques to characterize, identify, and quantitate a variety of constituents of complex biological and biochemical systems. This work is in collaboration with investigators in several Institutes.

Recent work has included the development of techniques to analyze trace levels of biologically important elements by flameless atomic absorption spectrophotometry and to localize these elements in subcellular structures of tissue by use of electron probe microanalysis. This work represents collaboration with investigators in NCI, NHLBI, and NIMH.

In collaboration with the Biophysics Laboratory of Creteil, France, the group has discovered accumulations of insoluble iron compounds in the kidneys of laboratory animals treated with successive doses of the anticancer drug cis-platin. The team is now attempting to determine whether this accumulation in the lysosomes of kidney cells causes one of the drug's major undesirable side effects. The group is also studying the kinetics of chemical species transformations at trace levels for platinum coordination compounds that are effective as anti-cancer drugs. The importance of this work is that it is the basis for rational development of improved clinical protocols for these very toxic drugs.

In a related study of cis-platin, with the Medicine Branch, NCI, the group is studying the distribution of chemical species of the drug in solution of systematically varied compositions. It is also studying the kinetics of the intra-species transformations to obtain improved clinical results and minimize toxicity. The kinetic effect is important because researchers have largely overlooked the low reaction rates of this complicated system, leading to treatments with unwanted side-effects. In collaboration with a renal physiology lab of the French Atomic Energy Commission in Saclay, France, the group has completed a study of the stability of chloride salts in quantitative elemental analysis of microdroplets (10^{-9} liter volume) using electron probe microanalysis. Collaborative work with the NIMH is continuing on analysis of trace levels of vanadium in the blood and cerebro-spinal fluid (CSF) of patients to determine the effects of the metal on enzymes in relation to manic-depressive behavior.

In collaboration with the NHLBI and the NIMH, the group is assembling a Secondary Emission Mass Spectrometer (SEMS) system to study particle-induced ionization of biological and high molecular weight compounds. The group has also initiated a systematic study of the energetics of various organic ions in relation to the different experimental conditions which occur in organic Secondary Ion Mass Spectrometry (SIMS) and Fast Atom Bombardment (FAB) analysis. The data reported on the energy distribution of secondary organic ions are an important contribution to the understanding of the mechanism of the ionization of labile compounds by bombarding particles, as well as a significant source of information which mass spectroscopists can use to optimize SIMS and FAB analysis. These data on the energy distribution of organic ions, including some alkaloids, are being reported for the first time. The group has also discovered novel applications of SIMS for analysis of specific compounds and has demonstrated a new approach to the analysis of mixtures of biological compounds using organic SIMS and tandem mass spectrometry (MS/MS). The SEMS instrument is also serving as a test facility for the development of ion sources and ion guns for mass spectrometers used in NIH intramural research.

The group and NIADDK have completed studies using analytical ultracentrifugation to determine the stoichiometry and association constants of the binding of plasmiogen to fibrinogen. Further collaborative studies relevant to fibrinolysis involve investigation of the binding of plasminogen to plasmin inhibitor and to the D and E fragments of fibrinogen. The team is also studying the self-association of such proteins as tryptophan synthetase and snake venom phospholipases.

Work with the Electrical and Electronic Engineering Section of BEIB on the computer-controlled data-acquisition system for the analytical ultracentrifuge has progressed well. The hardware for the system has been completed and its testing and the development of software are progressing simultaneously.

Electron Beam Imaging and Microspectroscopy Group

In the past year, the group has made significant improvements in the stability and sensitivity of the system, including the addition of automatic edge tracking to compensate for spectrometer drift, higher collection efficiency for the spectrometer, and numerous improvements in hardware and software.

In collaboration with the Laboratory of Cell Biology and Genetics, NIADDK, the Group is studying exocytosis in adrenal chronmaffin cells, the producers of epinephrine. This process serves as a useful model for the neuronal release of neurotransmitters. Distributions of carbon and nitrogen in chromaffin secretory granules have revealed structure which can be related to the distribution of actecholamines and other compounds in these cells. These studies have, until now, been carried out on freeze-substituted cells, but the group will soon use a cryo-transfer sample holder to investigate elemental distributions in sectioned, frozen-hydrated cells.

In another collaboration the Laboratory of Parasitic Diseases, NIAID, and BEIB obtained elemental distributions from erythrocytes that had been invaded by malarial parasites. The team has recorded images of nitrogen and iron that may provide information about the small excrescences sometimes visible on invaded red blood cell membranes (and by which the cells adhere to the inner lining of blood vessels).

In collaboration with the Pathology Branch, NHLBI, the Group has obtained both electron energy loss and x-ray emission spectroscopic images of lung macrophages lavaged from patients reportedly exposed to volcanic ash and beryllium. The collaborations found significant amounts of silicates and aluminosilicates in the sectioned cells, probably resulting from volcanic ash exposure.

Work on developing new methodologies has involved a combination of electron energy loss spectroscopy (EELS) and energy dispersive x-ray analysis (EDX). EELS is used to measure the total mass in the analytical volume, and EDX provides the mass of a particular element. A combination of the two gives the relative concentration, which is the quantity of interest in microanalysis. The Group has implemented new software to simplify the quantitation of EELS spectra.

The instrumentation of the group also includes a 50 keV electron beam microanalyzer, which is now connected in a preliminary way to the group's laboratory computer (PDP 11/60). Using this device, we have collaborated with NINCDS for most of this year to localize and image aluminum, silicon, magnesium, and calcium in the hippocampal region of brains of victims of Parkinsonian dementia, ALS, and Alzheimer's Disease. The effort has been highly successful: the group has produced clearly resolved images of these elements in neurons and axons. In addition, we have collaborated with the Clinical Pathology Department, CC, in an effort to quantitate and image the magnesium content of individual lymphocytes.

As an important component of its work to advance electronmicroscopy, the Group is working in several areas of computerized image enhancement, including pixel value estimation and controlled-parameter generation of images. Moreover, members of the Group, in collaboration with the Nuclear Medicine Branch, Clinical Center, have concluded the initial phase of work on linear, Gaussian, point-spread function (PSF) modeling of emission tomographic systems. This work will facilitate refinements in the design of emission tomographic scanners used for medical diagnosis.

Scientific Equipment Services (SES)

This group continues to provide scientific equipment, design, fabrication, repair, and rental service to the NIH scientific community. During FY 1983 and continuing into FY 1984, SES is attempting to increase the efficiency and range of services it provides.

SES is continuously updating shop equipment in order to provide more efficient service and keep abreast of changing technology. For example, a second numerically controlled milling machine on order will permit rapid fabrication of the unusually shaped molds used by our plastics shops. Since many of the new scientific instruments being purchased at NIH are controlled with microprocessors, we have also ordered an automated microprocessor troubleshooting system that will facilitate repair of these instruments.

A review of equipment sent to NIH's surplus depot has revealed a number of instruments that can be renovated. SES is undertaking a pilot study during which we will renovate some of this equipment and make it available to the NIH scientific community through BEIB's Scientific Equipment Rental Program.

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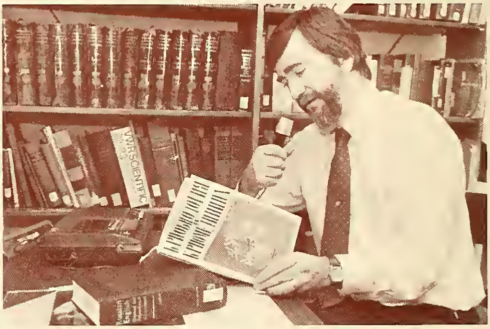


A few of the NIH Library's services for intramural investigators: biomedical literature in print form and microforms; translations; online automated catalog system with terminals for library users (1984).

Library Branch

Carolyn Brown, Chief

During much of this year, the NIH Library was involved in reconstruction and refurbishing. A new computer room of some 500 sq. ft. was built in a corner of the upper level reading room. New main entrance doors were constructed as part of the Clinical Center's fire safety remodeling. The entire Library got a fresh coat of paint, and new flooring (tile in the photocopy center, carpet squares in all other areas) was installed throughout.

Activities in preparation for automation of the catalog and circulation control were in progress throughout the year. A new computer and fourteen terminals were delivered and installed. Staff training on use of the new system consumed considerable amounts of time. Machine-readable records for all materials in the Library's collection were completed. The circulation system and on-line catalog were tested.

In preparation for the on-line catalog and in an attempt to deal with scarcity of space, a review of the journal and book collection, begun in 1982, was carried forward through much of the year. With the help of the Library Advisory Committee, the staff formulated a policy on journal retention periods and format. The principal theme of the policy is, "The NIH Library should commit itself seriously to the use of microform for storage, retrieval, reading and copy of pre-1955 journals . . . . Unless there is a compelling reason for a particular title to be held in another form, all pre-1955 journals that are to be retained by the NIH Library should be retained only in microform."

Following this policy, the Library tentatively selected titles to be withdrawn and advertised this selection through the Library Advisory Committee. Comments by NIH staff and use statistics on each journal allowed title-by-title decisions to be made. At the same time, the general book collection was subjected to a rigorous weeding. Selections of books to be withdrawn were placed in a special section of the lower level shelves for review by NIH staff, and each four weeks the greater portion of these books was removed from the collection. When the project was completed in September 1983, a total of almost 7,000 book titles consisting of 9,510 volumes had been withdrawn. In all, more than 18,000 volumes of books and journals were withdrawn from the collection in FY 1983, a far greater number than is usual.

The staff also evaluated the entire reference collection to replace outdated books with current editions and decide on retention policies. In general, certain biographical materials will be retained permanently; others will be retained from one to ten years. Only the current editions of directories with dated information will be kept. The Library will not hold more than the two most recent editions of specialized reference textbooks. Decisions were made on policy for retention of more than 460 titles in the reference collection.

The number of books purchased during FY 1983—approximately 3,000—was 30 percent higher than the 1982 figure. Programs to update the general book collection with continue through 1984 as funds become available. Microform will be obtained for those journals deemed unnecessary to retain in paper copy, and the paper copy will be withdrawn.

Library Services

The number of information requests remained relatively constant in the last two years. The staff responded to 14,700-15,500 reference inquiries per year and 6,800-7,500 requests per year for computerized bibliographic retrieval searches. Price increases for searching the on-line files have exceeded increases in funding, so limitations on number of years and files searched and restrictions on printing abstracts have remained in effect.

The hours of the Library's photocopy service were extended to 8 a.m. - 5:30 p.m., Monday through Friday, an increase of one hour and fifteen minutes daily. An additional photocopy machine was added for self-service use. These were efforts to reduce the lines waiting for photocopy. A new same-day photocopy service performed by staff was also put into effect. It is necessarily restricted to shorter articles.

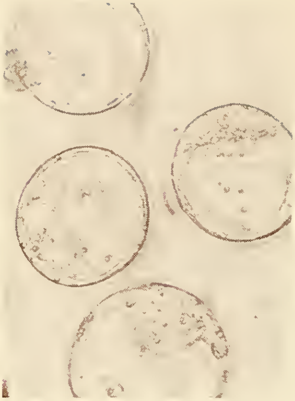
The Translation Unit was obliged to operate with only one translator for half the year. Now again fully staffed, the Unit has added the ability to translate into French or Spanish from English as well as the other way.

A guide book and information sheets on Library services were published during the year. Methods of access to Library service and descriptions of Library procedures are included in these bulletins, which are designed to simplify Library use.

Services of the NIH Library

The NIH Library offers a full array of services to assist scientific investigators in their work. They include:

- **Computer Bibliographic Searches** - Specialists perform computerized literature searches and compile bibliographies upon request. The staff is experienced in retrieving citations and abstracts from some 155 scientific data bases. (Request from Reference and Bibliographic Services.)
- **Current Awareness Service** - The Library's Selective Dissemination of Information (SDI) program provides users with regular computer updates on new literature in the biological and medical sciences. (Request from Reference and Bibliographic Services.)
- **Reference Services** - Reference librarians not only answer reference questions on site or by telephone (496-2184), but also advise users of other library services that may meet their needs.
- **Photocopying** - High speed photocopying machines are available to users. The Library also fulfills copying requests. (Photocopy Service.)
- **Microfilm and Microfiche** - Many journals are also kept in microform. Most are backfiles of important titles, acquired in order to save space. Reader-printers are located nearby.
- **Circulation** - Books other than reference works can be checked out. Second copies of certain journals are also available for circulation.
- **Interlibrary Loans** - Research publications not in the collection can be obtained from other libraries. Photocopies of journal articles obtained from the National Library of Medicine are usually provided in one to three workdays.
- **Translations** - Foreign language scientific materials are translated at request, and the translations are made available to other users as well.
- **Stacks Service** - Library staff will search for any volume a user cannot find on the shelves.
- **Monthly Acquisitions List** - This list, "Recent Additions to the NIH Library," is available in printed form and on the NIH Wylbur computer system.
- **Library Tours** - A tour with explanations of NIH Library services and policies is available every Wednesday at 2 p.m., beginning from the Reference Assistance Desk.
- **Carrels** - Private study carrels are available on a limited, first-come basis. (Circulation Unit.)



Laboratory animal science in the Veterinary Resources Branch (from top down):

A totally equipped central experimental animal surgery for use by intramural investigators.

Cryopreservation of rodent embryos for the NIH Genetic Resource.

Special procedures for maintaining defined laboratory animals.

Domestic production of primates for biomedical research. The owl monkey is essential for malaria studies.

The naturally athymic "nude mouse" (N:NIH (S)-*nu*), invaluable in immunology.

Veterinary Resources Branch

Robert A. Whitney, Jr., D.V.M., Chief

The Veterinary Resources Branch (VRB) provides professional and technical support services for NIH intramural programs. It is responsible for

- Production of defined research animals
- Procurement, quarantine, conditioning, and Issuance of animals from outside sources
- Management of a central animal surgery and radiology facility
- Animal disease diagnosis and control
- Research holding for primates, cats, dogs, and livestock
- Consultative services on animal health, care, husbandry, genetics, and nutrition
- Maintenance of an international laboratory animal Genetic Resource
- Admininstrative support of the Interagency Research Animal Committee.

While continuing to meet all of these responsibilities, the Branch also increased its involvement in activities to strengthen laboratory animal use and care programs both within NIH and throughout the Federal government.

VRB staff took the lead in developing an NIH manual issuance stating policies and procedures in this regard for intramural research programs. The document, which will become part of the NIH Manual in FY 1984, ensures consistency of approach in intramural and extramural activities involving laboratory animals. The subjects covered include the makeup and activities of Animal Care Committees in the BIDs and of the NIH-wide Animal Care Committee, whose members are the chairpersons of the BID committees. For many years VRB has provided the NIH Animal Care Committee with the services of its executive secretary, and the Chief of the VRB has served as committee chairman.

VRB has also provided the executive secretary and staff support for the Interagency Primate Steering Committee since its inception; an expanded role and name change for that committee further broadens the Branch's contributions to laboratory animal science. In July 1983, the Assistant Secretary for Health renamed the Interagency Primate Steering Committee as the Interagency Research Animal Committee and expanded its functions, making it a focal point for discussing issues concerning the care, use, and conservation of all nonhuman vertebrate animals used in Government research. In keeping with its expanded mission, additional Federal agencies were also added to the Committee's membership. Because of the special value and short supply of primates, the new committee will continue to monitor national and international trends in the use of nonhuman primates for biomedical research and testing. Contracts with the World Health Organization and the Pan American Health Organization were continued to assist Latin American and Asian countries to develop national primate programs.

In VRB's operations providing products and services to NIH intramural researchers, several programs were modified to increase efficiency and minimize costs.

Small Animal Section

A new service which the Small Animal Section (SAS) began to offer this year meets a long-felt need of NIH intramural research programs. SAS now provides holding of rodents and rabbits during research projects. Renovations in Building 14B have enabled SAS to provide 6,300 square feet of space for this purpose. Investigators conducting research in pharmacology, pregnancy, dental caries, and immunology were the first to make use of the holding service.

In a reorganization of the Section, a Research Support Unit was established to provide technical and supportive services for the new holding operations. Three SAS units were consolidated to form the Research Support Unit and the Production Unit. In the same reorganization, the name of the Cagewash Unit was changed to Equipment Sanitation Unit.

The Small Animal Section's principal functions are to provide rodents and rabbits from its production colonies and to manage contracts for this purpose. It manages a Genetic Resource containing more than 200 defined strains and has programs devoted to animal model development, nutrition, and health.

Demand for small animals decreased. Approximately 170,000 rodents and rabbits from SAS colonies and 500,000 from contract sources were issued for use in NIH research programs (Fig. 1). This is an overall decrease of 20 percent from the numbers issued in 1982.

The composition of the Genetic Resource was virtually unchanged. Inbred hamsters (LSH/TrN) and rats (LER/N), were introduced, and one rat strain (A990/N) was lost to reproductive failure. Forty-one mouse strains previously infected with mouse hepatitis virus were rederived into the barrier area. Fourteen additional strains and stocks of mice, rats, hamsters, and rabbits are awaiting introduction, and requests to introduce numerous others have been deferred because space is not available. An NIH Animal Genetic Resource Advisory Committee was established to assist in developing guidelines for the introduction, maintenance, and deletion of strains in the Resource's barrier. The Section's embryo cryopreservation program is devoting its efforts to preserving embryos from strains that have potential value in research but are not currently used, as well as embryos from strains that are in high demand. The latter will make it possible to rapidly "reconstitute" colonies affected by disease or genetic contamination, and periodic use of these embryos will also retard genetic drift.

The Production Unit moved its non-barrier mouse colonies to a central location to increase efficiency and decrease the probability of genetic contamination. New lighting systems were installed to increase the level of environmental control in all of the rodent and rabbit breeding colonies.

The SAS nutrition program provided investigators with information and assistance on experimental diets and developed specifications for the procurement of standard laboratory animal diets used at the NIH. A new open-formula diet for macaque monkeys became available, and studies began on developing and evaluating an open-formula diet for callitrichids.

In collaboration with the Comparative Pathology Section, SAS investigated the occurrence of two problems in guinea pigs: an increase in mortality among neonates—characterized by pulmonary atelectasis, malocclusion, and inanition—and various reproductive disorders in preparturient and postparturient sows. Vitamin inadequacies in some batches of feed were detected and are postulated to be a contributing factor. Cecitis emerged again as a major cause of death in the rabbit colony but, as in previous outbreaks, the cause remained elusive.

Evaluations were made at the invitation of the National Eye Institute (NEI), National Institute of Dental Research (NIDR), and National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) concerning their animal care programs and facilities, and a staff veterinarian was appointed to serve on the Animal Care Committee of the NIADDK.

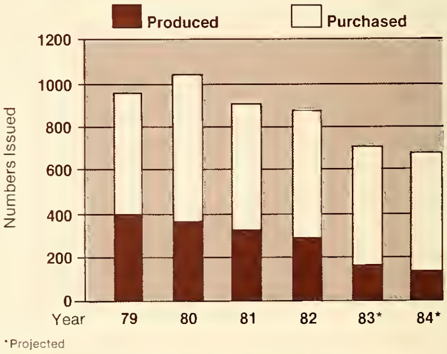
A contract was awarded to develop and install a data management system to enhance the capability and efficiency of breeding, maintenance, research holding, censusing, and disease surveillance in the Section's colonies, thereby better serving the needs of NIH for research animals.

Animal Center Section

The NIH Animal Center in Poolesville, Maryland, acquires, produces, maintains, and develops large laboratory animals and provides related services and products for NIH investigators. Species involved are dogs, cats, nonhuman primates, and livestock. Breeding colonies provide defined foxhounds, beagles, pointers, miniature swine, and monkeys; various other animals are purchased, quarantined, and conditioned for NIH research.

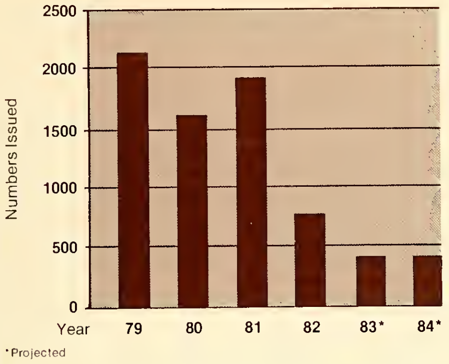
The Primate Quaratine Unit was renamed the Primate Unit to reflect program changes. Procurement, quarantine, conditioning, and subsequent issues of nonhuman primates have markedly declined during the past two years (Fig. 2), and this function has been largely replaced by research holding of monkeys that are on study (Fig. 3). Facilities and services are currently provided to support research conducted by various NIH Institutes. Other breeding activities at the Animal Center include developing a colony of moustached tamarins (*Saguinus mystax*) for hepatitis research conducted by the National Center for Drugs and Biologics. In addition, a breeding colony of rhesus monkeys (*Macaca mulatta*) is maintained at Perrine, Florida, to provide animals for a variety of intramural research programs. The overall rhesus breeding program, however, has been reduced dramatically within the past year to reflect the reduced needs of NIH

Figure 1.
Rodents and Rabbits Issued



*Projected

Figure 2.
Nonhuman Primate Issues



intramural investigators and to improve the financial position of the program.

Populations of livestock maintained by the Ungulate Unit continued at previous levels, and the use of blood and blood products stabilized. A colony of inbred miniature swine continues to be developed and maintained for the National Cancer Institute (NCI) studies in transplantation immunology, and excess animals are being provided to other institutions when available. Support and services are also being provided for a colony of swine used by the National Heart, Lung, and Blood Institute (NHLBI) in atherosclerosis studies.

Modifications continued in the Carnivore Unit program to adjust to current and projected research utilization of cats, dogs, and canine blood. NIH utilization of foxhounds stabilized, and the use of beagles from the breeding colony maintained for NCI has increased (Fig. 4). Issues of canine blood have decreased to one-tenth of the numbers of units provided during the 1970's, and appropriate adjustments were made in the size of the donor colony. There has also been a trend towards less utilization of long-term holding services provided for dogs and cats.

A number of collaborative research projects using nonhuman primates were undertaken with investigators form the National Institute of Child Health and Human Development (NICHD), NIADDK, NEI, NIMH, and NHLBI. These involved studies of endocrinology behavior, atherosclerosis, nitrition, and reproduction. Reproductive difficulties associated with the inbreeding of miniature swine are being studied by scientists from VRB, Clemson University, and the National Zoological Park in an effort to enable perpetuation of these animals for immunological studies.

Figure 3.
Nonhuman Primate Holding Days

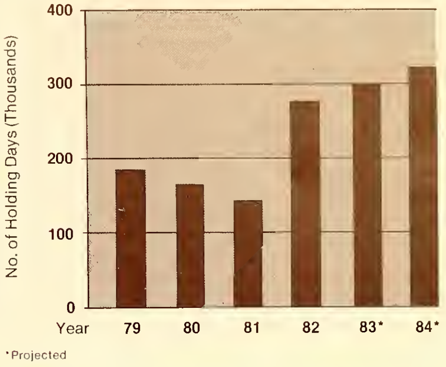
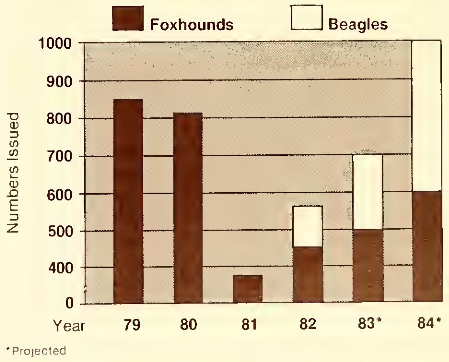


Figure 4.
Purebred Dog Issues



Comparative Pathology Section

The Comparative Pathology Section (CPS) characterizes the health status of laboratory animals produced, quarantined, or used at NIH. It studies naturally occurring diseases and the measures necessary to prevent or control them. The Section also maintains a program for ensuring the genetic definition of rodents produced by VRB for NIH research programs or for use as breeders by other institutions.

The number of necropsies performed by the Pathology Unit continued to increase, primarily because of intensified efforts to determine the cause of death for all animals from VRB colonies.

Deaths among guinea pigs in the Small Animal Section contributed to the increase. (See page 22.)

The number of samples cultured by the Microbiology Unit increased by 22 percent because of a greater need for microbiologic investigations connected with diagnotic pathology. Samples submitted for parasite and virus monitoring and for hematology were approximately the same as previous years.

Utilization of the Animal Disease Investigation Service (ADIS) increased by 14 percent; diagnostic services provided for numerous primates maintained by the Primate Unit for NIH investigators contributed to this increase. The ADIS also undertook responsibility for coordinating a campus-wide rabies surveillance and control program. VRB staff members, in conjunction with personnel of the Grounds Maintenance and Landscaping Branch and the NIH Police, are responsible for capturing wildlife and domestic animals suspected of being rabid and submitting them for laboratory diagnosis.

Permits to introduce rodents and rodent products into the NIH were issued at a level 50 percent higher than in 1982. Ten of them required that rodents be quarantined before their release into Institute research colonies. Hantaan virus, the etiologic agent of Korean Hemorrhagic Fever, was added to the list of agents to be tested for in imported rats, because of human infections contracted from contact with laboratory rats in some foreign countries.

There was little change in the number of mice and rats from the foundation and pedigreed expansion colonies of the Genetic Resource monitored by the Genetics Unit. However, the Genetic Investigation Service conducted studies on two genetic contaminations which occurred in the NZW/N production colony. Investigation of genetic problems involving Institute research animals was at the same level as the last two years.

Two important advances in laboratory methodology were made by the Microbiology Unit. One was the propagation of *Bacillus piliformis,* the agent of Tyzzer's disease, in tissue culture; and the other was the propagation, in hens' eggs, of the cilia-associated bacillus of rat lungs.

Veterinary Medicine and Surgery Section

The Veterinary Medicine and Surgery Section (VMSS) maintains facilities for experimental surgery and for holding large research animals, and it provides comprehensive services covering the care and use of these species.

Caseload in the Surgery Unit has increased from 750 in 1980 to more than 1200 in 1983. Efforts were directed this year towards developing procedures in fetal surgery to permit the study of prenatal physiological anoxia and circulation and of fetal growth and development.

The Comparative Medicine Unit houses dogs, cats, and small species of livestock. Professional and technical support was provided to maintain piglets in isolators for rotavirus studies, and to maintain dogs used to investigate cancer chemotherapeutic agents and intraoperative radiation therapy. The Unit also provides postoperative management for animals recovering from surgery. Populations of animals maintained by the Unit declined slightly from the levels of previous years.

The Primate Research Unit provides research holding for over 900 nonhuman primates and operates the primate recycle program whereby animals are issued from one study to another for conservation and economy. The Unit provides professional and technical services directed towards producing time-pregnant monkeys for investigators and provides postoperative care. Major research efforts supported by the Unit include cardiovascular studies conducted by NHLBI and malaria research performed by NIAID.

Outlook for 1984

Provision of animals and related services is expected to stay at or near the levels of FY 1983, and program adjustments will continue so that the Veterinary Resources Branch can improve its response to NIH needs for services at minimal cost. The initial phases of a computerized system to assist in managing animal colonies maintained in the Branch is expected to be installed. It is anticipated that the Branch will participate further through the Interagency Research Animal Committee in identifying and proposing solutions to issues concerning the care and use of animals in Government research.

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The Interagency Research Animal Committee (IRAC)

Thomas L. Wolfle, D.V.M., Ph.D.
Executive Director

On July 7, 1983, the Assistant Secretary for Health, DHHS, created the Interagency Research Animal Committee (IRAC) as an outgrowth of the Interagency Primate Steering Committee (IPSC), reflecting the growing need for a Federal interagency committee knowledgable about the conservation, use, care, and welfare of research animals. In the nine years since the birth of the IPSC the focus of the Committee has been almost exclusively on nonhuman primates—with one notable exception. The United States was invited to send as an official observer to the Council of Europe deliberations on drafting a convention on the use of animals for scientific purposes, and later was provided the opportunity to establish a formal position on the draft convention. Because of the potential impact of the convention on the exchange of test data and drugs between the United States and European countries, input from the United States was important. The IPSC, as the only Federal interagency committee concerned with research animal issues, formed an ad hoc subcommittee for this purpose and drafted the document that later became the official United States position. By performing this function, the IPSC ensured that the United States position reflected the point of view of many agencies involved with research animals. This activity underscored the growing need for a focal point for Federal agencies to deal with many issues involving all animal species needed for biomedical research and testing. Thus, it was logical that the IPSC's mission be modified and its membership extended for this purpose.

To appreciate the new responsibilities of the IRAC, it is important to understand both the nature of its predecessor's involvement in biomedical research and testing and the value of nonhuman primates to these programs.

Evolution of the Interagency Primate Steering Committee (IPSC)

Currently leprosy and acquired immunodeficiency syndrome (AIDS)—one very ancient and one very new disease—are both being reported with increasing frequency in the United States. These diseases represent two devastating afflictions of mankind in which recent study in nonhuman primates holds promise for their eventual cure or prevention. These uses are but recent examples of a long list of conditions for which primates have played a key role in the discovery of disease processes; some notable examples are the development of vaccines for hepatitis B and poliomyelitis. The continuing supply of these valuable animals—a prerequisite which the biomedical research community has learned not to take for granted—is thus critical to the further understanding and elimination of these and other diseases of man.

Until the early 1970's most species of nonhuman primates were readily available from the wild. Their continuing important role in biomedical research was assured on the basis of historical precedents, existing baseline data, cost, availability of research funds, and investigators' anticipated requirements. It was therefore seen as a severe threat to the future health of this country and other peoples of the world when, within a five-year period between 1973 and 1978, exports of primates were banned by three countries which supplied 70 percent of the primates imported into the United States.

In response, in October 1974, the Director of the National Institutes of Health established a steering committee to develop a unified approach to assure both short- and long-term supplies of primates critical to biomedical research, testing, and vaccine development programs. The following year the Assistant Secretary for Health, Department of Health, Education, and Welfare, expanded the committee to include the following agencies:

Centers for Disease Control
Department of Defense
Environmental Protection Agency
Office of International Health
National Center for Drugs and Biologics, FDA
National Institute of Mental Health
National Science Foundation
Veterans Administration

The National Institutes of Health was established as the lead agency, and the Director of the NIH Division of Research Services was appointed Chairman of the Interagency Primate Steering Committee (IPSC). The Department of Interior was added later as an observer, and the Executive Director and staff support were provided by the Veterinary Resources Branch, DRS.

Response by the IPSC to Short-Term Supply

Shortly after its formation the IPSC concluded that the establishment of breeding colonies in the United States was an important first step. The

Committee was instrumental in the establishment of several breeding colonies administered by member agencies and private industry. Animals from these colonies alone accounted for 28 percent of the total number of newly acquired primates by researchers in 1981 (7,780 of 28,256).

Since many primates or their tissues are usable for more than one project, the idea of recycling was conceived by the Committee. In 1977 the Division of Research Resources awarded a contract to the University of Washington Regional Primate Center for the management of a Primate Supply Information Clearinghouse (PSIC), which in 1981 was instrumental in the reissue of 16 percent (4,596) of the total newly required primates in the United States. The PSIC and the domestic breeding colonies together provided 44 percent (12,376 of 28,256) of the primates entering research programs in 1981. Because of increasing production and recycling and decreasing numbers imported, by 1984 close to 60 percent or primate requirements for biomedical research will come from these domestic programs.

Long-Term Supply

While it became clear that domestic programs were the key to providing essential primates for biomedical needs in the United States, there was at the time a sense of obligation to initiate programs of conservation in source countries. These countries provided primates not only for research but also for the domestic breeding colonies being established. Furthermore, the Committee realized that many primate species were (or soon would be) listed as endangered under the United States Endangered Species Act. This closely parallels the listing by the Convention on International Trade in Endangered Species (CITES), which in 1977 included all primate species either in Appendix I or II, resulting in strict trade guidelines by signatory countries.

Although the eighty CITES member countries have agreed to protect and foster indigenous populations of animals, the pressure for tillable land and the traditional hunting of larger primates for food continue to take precedence in many developing countries over the value of primates as threatened or endangered species. The conversion of forest habitats to agricultural land was an is taking place on a massive scale.

The Committee felt that if these endangered animals—so valuable to the health of mankind—are to be saved in the long run, a sense of awareness and a new technology must be introduced into source countries. Accordingly, the IPSC supported the initiation of contracts and interagency agreements for the purpose of training biologists of developing countries in wildlife management, forestry, and habitat conservation. LANDSAT imagery of forest habitats was provided to field workers, and study of the demographics, breeding, and resocialization of the United States chimpanzee population further served to identify the fragility of these unique and valuable animals. Contractual programs with the World Health Organizaton and Pan American Health Organization were developed for these international programs.

The programs of the IPSC have succeeded in their intended goals. Domestic production is becoming increasingly a private enterprise, with the IPSC assuming more of an advisory and monitoring role. Training programs in this country and abroad have produced the needed technology for cooperating countries to continue their programs, enabling IPSC involvement to become more consultative than programmatic.

A Sense of Continuing and Expanding Responsibilities

This dicussion has said little about the role of non-primate animals in biomedical research, yet that role is considerable; these animals continue to add to our knowledge of cancer, heart disease, genetics, diabetes, aging processes, neurological disorders, and many others.

The birth of this expanded committee acknowledges the continuing value of all animals for biomedical advancement; virtually every major biomedical breakthrough of this century has depended upon the contributions of research animals. However, public concern for the welfare of all animals is increasing. Continuing improvements must be made in housing, and research protocols must ensure humane care and scrupulous selection of the most appropriate species or non-animal alternative.

The IRAC is charged with being responsive and sensitive to these values and will work vigorously to support and extend the use of animals in mankind's behalf while also seeking new knowledge which will continue to increase the quality of care provided. With the addition of the National Aeronautics and Space Administration and the Department of Agriculture to IRAC, its member agencies, working together, can play an important role in the coordination of supply, utilization, welfare, and conservation of all research animals.

Medical Arts and Photography staff help NIH investigators record and report their research (from top down):

A medical illustrator at work.

A medical cimematographer edits film of a surgical procedure.

A computer-generated poster title is prepared.

Posters, programs, and publications are designed for NIH conferences.

Photomacrography of a medical model produced by the Medical Illustration Section.

Medical Arts and Photography Branch

Ronald B. Winterrowd, Chief

The Medical Arts and Photography Branch (MAPB) documents NIH investigators' scientific data through photographs and graphic illustrations for publication in journals or for presentation at scientific or lay meetings. MAPB also supplies various other NIH information needs.

Budget constraints and inflation remain MAPB's paramount concern. While continuing to provide the service and hold down costs as it has in the past, the branch has proved it can handle any project and produce top quality work with seemingly impossible-to-meet short due dates. But now MAPB must search for still more ways to contain or cut production costs. In the Branch's initial effort last year, overall costs were cut by 25 percent. This year, however, Graphics has cut costs by 6 percent, Photography has risen only 2.7 percent, and Design costs are down 9.6 percent. This year's efforts represent still further savings of 12.9 percent overall reductions.

The Branch's staff of 49 artists, photographers, and other specialists has extensive expertise in converting data into effective presentations. They are highly skilled in meeting the needs of scientists for graphic presentation, medical arts, and still and motion picture photography, including photomacrography and photomicrography. Services include design and production of publications; preparation of slides, vugraphs, and other projected visual aids; animation artwork; technical, general, and medical illustrations; exhibit design; statistical drafting; display charts; posters; and medical models.

The philosophy of the Branch is to provide high quality professional services competitive in cost with commercially obtainable services. On contracted work, the staff works closely with vendors of graphic and photographic services to ensure that MAPB's quality standards are kept.

To reduce users' costs while maintaining productivity and product quality, MAPB has set up an educational program on cost awareness and cost reduction within the NIH community. It stresses the savings in money and time that investigators can derive by thinking through in advance how they want their articles and presentations illustrated, discussing their requirements with MAPB at an early stage, and adhering to their plan once it has been made.

Investigators are advised to submit complete, clear, and accurate raw data for display as early as possible. Careful planning can eliminate two causes of expense: 24-hour rush service to meet a deadline, and changes in artwork that has been prepared in final form. Rush service costs 50 to 100 percent more than regular, and changes or corrections of final artwork can double its cost.

Staff members also ask investigators to order only the necessary number of slides and pictures, and inform them about how to protect artwork for future reprinting; replacement of damaged materials can be as costly as the original.

In another effort to contain costs, the Graphics Unit requires bids on all contract work, even though procurement regulations require negotiations only for bids over $500.00.

Photography Section

The Photography Section's requests for services increased by 16.3 percent during the year. Photography support services in photomicrography, photomacrography laboratory work, and technical information were provided to NIH investigators by highly trained photography technicians using advanced printing and processing equipment. To supplement our inhouse facilities, the section continued to obtain the services of vendors in the Washington, D.C. area.

Motion Picture Section

The number of filming requests has increased in 1983, with five formal productions completed in this year.

Design Graphics Section

This section is composed of a group of professionally trained, highly skilled and experienced designers and illustrators. Many have won awards in local, national and international competitions. The NIH scientific community relies on this section to provide graphics for a wide variety of uses both in scientific presentations and in public information: technical illustrations, publications, posters, exhibits, and slides. This includes the design and preparation of support materials for various conferences organized at the NIH.

Medical Illustration Section

This section is staffed with talented, highly trained artists who possess a broad background in medical science. Their workload remained constant, with a trend toward surgical illustrations for journal articles and other scientific papers, slides, medical atlases, and other longer-term projects.

Outlook for FY 1984

In the new fiscal year the Branch will offer two new services by the Graphics Unit and Photography Section. The Graphics Unit will enlarge its computer graphics capacity by adding the production service of computer generated color slides, and the benefits of this service will be many. Slides will be produced at lower prices, requestors will no longer have to store black/white board art, the system will store the information for the requestor on floppy disk, and if a change is needed at a later date the disk can be pulled and revised. Also available are black and white slides from which prints can be made to be sent to publishers.

The Photography Section will be offering the new service of video micrography. A new video camera and recorder will produce an instant image on ¾ inch tape. The adaptation of time-lapse video offers many possibilities including the viewing of cell development, the growth of bacteria, or even cell division. Because there is no delay for film development, video micrography provides the viewer an immediacy not previously available.

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biomedical research project: planning, making available models and substrates, manipulating and measuring research materials, and recording and communicating research results.

- The Library Branch possesses or has access to virtually all published biomedical knowledge to assist the investigator in planning and designing his/her project.
- The Veterinary Resources Branch provides the animal models, organic materials, and proper facilities for their use.
- The Biomedical Engineering and Instrumentation Branch collaborates with the investigator in devising the means whereby research materials may be manipulated and results measured, often with highly sophisticated electronic equipment.
- Finally, the skills of the Medical Arts and Photography Branch are available to all investigators to enable them to record the results of their research and communicate them to the scientific community.

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